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INTERACTION OF THE ANTI-CANCER DRUG SULFORAPHANE WITH DMPC MODEL LIPID MEMBRANES

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Sulforaphane (SFN) is a phytochemical compound that is being actively studied due to its potential anti-cancer and antibacterial properties. It is found in cruciferous plants of the cabbage family, such as broccoli, cauliflower and kohlrabi, and is the subject of intensive research, especially in the field of oncology. It is known that the interaction of anticancer drugs with cell membranes plays a critically important role in their entry into the cell, intracellular accumulation and, ultimately, in their pharmacological activity. Nevertheless, the multicomponent composition and complexity of the architecture of biological membranes significantly complicate the study of these molecular interactions. To overcome these difficulties, simpler systems such as model lipid membranes are often used as experimental models. Since the effect of SFN on the structure of cell membranes is still unexplored, a study of its interaction with model lipid membranes has been conducted.

In this work, the systems of natural (aqueous solution of broccoli extract –SFN1) and synthesized (1-isothiocyanato-4-(methylsulfinyl)butane –SFN2) sulforaphane with monolayer phospholipid vesicles DMPC (1,2-dimyristoyl-sn-glycero-3-phosphocholine) at different lipid/sulforaphane ratios (10/1 and 50/1).

Various options for the arrangement of the sulforaphane molecule relative to the hydrophilic and hydrophobic parts of the lipid molecule were considered. Quantum chemical calculations of the optimal bonding geometry of DMPC and SFN lipid molecules have shown that in the most energy-efficient cluster, the sulforaphane molecule is located near the lipid head and perpendicular to its tails, while a hydrogen bond (1.8 Å) is formed between the oxygen of the SO group of sulforaphane and the hydrogen of the CH2 group of the lipid head (Fig. 1a).

According to IR spectroscopy data, conformational changes induced by SFN in the DMPC bilayer are noticeable in areas sensitive to the state of acyl chains (2800-3000 cm-1) and polar heads of lipids (Fig. 1b). The frequencies of symmetric and asymmetric stretching of the PO2-functional group practically do not change when SFN is added to DMPC. Changes in the band widths of the PO2–group (broadening for symmetrical, narrowing for asymmetric) indicate a complex change in the dynamics and heterogeneity of the environment of phosphate heads, and may be due to the fact that SFN, being partially immersed, changes the hydration shell of phosphate groups and their conformational dynamics. Analysis of the valence vibrations of the methylene (CH2) and methyl (CH3) groups in the region of 2800-3000 cm-1 showed a narrowing of these bands, indicating an increase in the ordering and/or a decrease in the conformational heterogeneity of lipid acyl chains in the hydrophobic core of the membrane by the influence of SFN. The most significant changes related to SFN localization were found in the region of valence vibrations of the isothiocyanate group (-N=C=S) of sulforaphane itself, which is characterized by two intense bands of 2107 and 2181 cm-1 for symmetrical and asymmetric stretching, respectively. There was a significant shift of the 2107 cm-1 band by 8 cm-1 towards higher wave numbers. (up to 2115 cm-1). This indicates that the isothiocyanate group has moved to a less polar, more hydrophobic, and/or more sterically restricted environment. The only such medium in this system is the inner part of the DMPC lipid bilayer. Based on changes in the IR spectra, it can be assumed that sulforaphane is embedded in the DMPC lipid bilayer. This conclusion is in good agreement with the optimal geometry of DMPC and SFN lipid molecules obtained using quantum chemical calculations.

Structural studies of the DMPC, DMPC/SFN1 and DMPC/SFN2 systems were carried out using small-angle X-ray scattering (SAXS) at the XEUSS 3.0 station (Fig. 2a). The scattering curves were modeled using the three-layer shell core model in the SasView program. The internal radius of the vesicles (R = 211,8 ± 1,2; 209,9 ± 1,2; 216,8± 0,4; 220,5 ± 1,0 Å) and the thickness of the lipid bilayer (T = 38,6 ± 2,4; 38,7 ± 0,2; 38,3 ± 0,9; 38,9 ± 2,8 A) for pure lipid, lipid with SFN1 and lipid with SFN2 (DMPC/SFN = 50/1 and 10/1), respectively. It is worth noting that an increase in the concentration of sulforaphane leads to the fusion of vesicles, as evidenced by the appearance of a peak at q = 0.12 nm^{-1}, which corresponds to the average distance between adjacent bilayers of 53.8 nm. In the wide-angle region of the scattering curves, an increase in peak intensity is observed with an increase in SFN concentration (Fig. 2b). This indicates a greater ordering of the hydrocarbon tailings and is consistent with the results of the FTIR mentioned earlier.

The obtained results of the interaction of sulforaphane with model single-layer vesicles are important for un-

derstanding the effect of this anticancer compound on the structure and biological functions of cell membranes.

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